IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re:

Inventors:	Tanner et al.	Atty. Docket No.:	RPS6098D1-US
Serial No.:	10/821,538	Examiner:	Joseph S. Del Sole
Filing Date:	April 9, 2004	Art Unit:	1722

Entitled: ENCAPSULATION MACHINE WITH VALVED INJECTION WEDGE

CERTIFICATE OF MAILING UNDER 37 C.F.R. §1.6(d)

Date of Deposit: 7/25/05

I hereby certify that this Respons, Terminal Disclaimer with Fee Transmittal and IDS are being sent via facsimile to the attention of Examiner Joseph S. Del Sole at (703) 872-9306 in care of Commissioner for Patents, MAIL STOP – AF-FEE, P.O. Box 1450, Alexandria, Virginia 22313-1450.

Jennifer Warner

INFORMATION DISCLOSURE STATEMENT

As authorized and encouraged under 37 C.F.R. §§1.97-1.98 and the provisions of MPEP §§609 and 707.05(b), Applicants submit herewith certain patent references, publications and/or other information which the Patent and Trademark Office may wish to consider in examining the above-identified patent application. These references and information are listed below and on attached form PTO-1449.

U.S. PATENT DOCUMENTS

None

FOREIGN PATENT DOCUMENTS

None

OTHER DOCUMENTS

1. "The Theory and Practice of Industrial Pharmacy", Lachman, Lieberman and Kanig, Third Edition, pp. 399-407

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The identification of any document herein is not intended to be, and should not be understood as being an admission that each such document, in fact, constitutes "prior art" within the meaning of applicable law.

Applicants submit this statement in accordance with their duty of disclosure under 37 C.F.R. §1.56. This statement is filed in accordance with 37 C.F.R. §1.97(b)(3), before the mailing date of a first Office Action on the merits. Therefore, it is believed that as a result of no action being taken on this file as of the filing date of this disclosure, no fee is due by Applicant.

Applicant respectfully requests that the documents cited herein be made of record in the normal manner and that such documents appear on the printed patent as being considered and made of record.

Respectfully submitted,

Dated: July 25, 2005

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FORM PTO-1449 TO BE FILED WITH THE
INFORMATION DISCLOSURE STATEMENT

U.S. Department of Commerce
Patent and Trademark Office

Docket No.: RPS6129-US Serial No.: 10/821,538

Tanner et al.
Applicant

INFORMATION DISCLOSURE
STATEMENT BY APPLICANT

April 9, 2004
Filing Date

1722
Group Art Unit

Joseph S. Del Sole
Examiner's Name

U.S. PATENT DOCUMENTS

None

FOREIGN PATENT DOCUMENTS

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Examiner:_____ Date Considered:_____

Examiner: Initial if citation considered, whether or not citation is in conformance with MPEP §609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.

The identification of any document herein is not intended to be, and should not be understood as being an admission that each such document, in fact, constitutes "prior art" within the meaning of applicable law since, for example, a given document may have a later effective date than at first seems apparent or the document may have an effective date which can be antedated. The "prior art" status of any document is a matter to be resolved during prosecution.

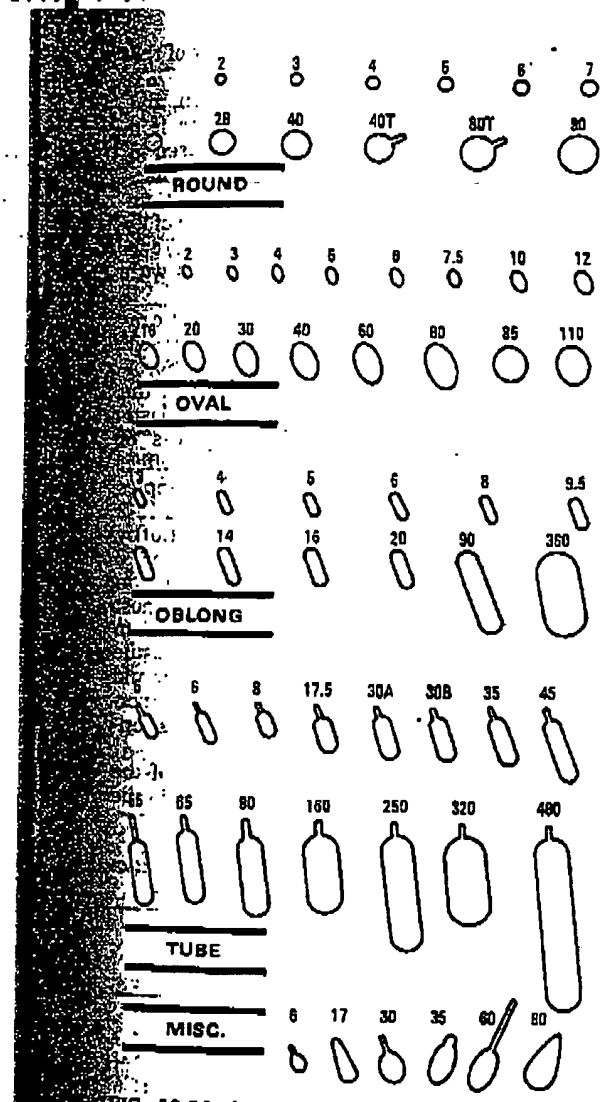

FIG. 13-26. *Sizes and shapes of soft gelatin capsules (1 cc = 16.23 m). Numbers represent the nominal capacity in minims. (Courtesy of R.P. Scherer Corporation, Troy, MI.)*

invented the *rotary die process*. Prior to this invention, soft gelatin capsules were not looked on favorably by the pharmaceutical industry, owing to the relatively large amount of the capsulated material (15 to 20%) lost during manufacture, and to the variation in the net content of the capsule (possibly 20 to 40%). The rotary die process reduced manufacturing losses to a negligible figure and content variation to less than ±3%. The Scherer machine cannot be purchased or leased, but the Scherer organization provides plant and laboratory facilities for the manufacture of this dosage form in the United States and nine foreign locations.

The early success of the rotary die process led others to develop continuous methods of soft gelatin capsule manufacture. One such method, known as the *reciprocating die process*, was announced in 1949 and was developed by the Norton Company, Worchester, MA. Another continuous process, also announced in 1949, was developed by the Lederle Laboratories Division of the American Cyanamid Company and has been used solely in the manufacture of that company's products. This equipment, known as the *Accogel machine*, is unique in that it is the only equipment that accurately fills powdered dry solids into soft gelatin capsules.

A discussion of the comparative advantages and disadvantages of the foregoing four processes—plate, rotary die, reciprocating die, and Accogel machine—is beyond the scope of this chapter and would have little instructive value, since the pharmaceutical chemist seldom has the opportunity to choose between the four types of equipment. One must consider, however, that for maximum production efficiency, the continuous processes demand almost 24 hours per day, 5 (preferably 7) days per week, of continuous operation. Thus, medicament formulations must be so designed as to maintain their desired physical characteristics during this period of operation as well as during periods of weekend shutdowns, should they occur. The production capacity of each of these machines is determined by (1) die size, which determines the number of die pockets on the standard-sized die plate, rotary die, or reciprocating die; (2) the speed of the machine (of the operators for the plate process); and (3) the physical characteristics of the material to be capsulated. Formulations are designed to achieve maximum production capacity consistent with maximum physical and ingredient stability and therapeutic efficacy.

All of the aforementioned equipment is limited to the production of gelatin capsules. Other films and film-forming polymers have not as yet been successfully adapted for use on these machines. An interesting review of the patent literature, covering capsule technology, has been published.[2]

The Nature of the Capsule Shell

The capsule shell is basically composed of gelatin, a plasticizer, and water; it may contain additional ingredients such as preservatives, color-

ing and opacifying agents, flavorings, sugars, acids, and medicaments to achieve desired effects.

Gelatin's chemical, physical, and physiological properties make it an ideal substance for the capsulation of pharmaceutical products.[3-6] The *gelatin* is USP grade with additional specifications required by the capsule manufacturer. The additional specifications concern the Bloom strength, viscosity, and iron content of the gelatins used.

The *Bloom* or *gel strength* of gelatin is a measure of the cohesive strength of the cross-linking that occurs between gelatin molecules and is proportional to the molecular weight of the gelatin. Bloom is determined by measuring the weight in grams required to move a plastic plunger that is 0.5 inches in diameter 4 mm into a 6⅔% gelatin gel that has been held at 10°C for 17 hours. Bloom may vary with the requirements of the individual custom manufacturer but ranges from 150 to 250 g. In general, with all other factors being equal, the higher the Bloom strength of the gelatin used, the more physically stable is the resulting capsule shell. The cost of gelatin is directly proportional to its Bloom or gel strength and thus is an important factor in the cost of soft capsules. Consequently, the higher Bloom gelatins are only used when necessary to improve the physical stability of a product or for large capsules (over 50 minims), which require greater structural strength during manufacture.

Viscosity of gelatin, determined on a 6⅔% concentration of gelatin in water at 60°C, is a measure of the molecular chain length and determines the manufacturing characteristics of the gelatin film. The desired film characteristics are usually based on standard gelatin formulations, which allow production at a set sealing temperature and definite drying conditions, and produce a firm, nontacky, nonbrittle, pharmaceutically elegant product. The viscosity for gelatin can range from 25 to 45 millipoise, but the individual manufacturer sets a narrow range, e.g., 38 ± 2 millipoise, for a particular type of gelatin, to make use of a standard formulation and thus conform to standard production conditions.

Low-viscosity (25 to 32 millipoise), high-Bloom (180 to 250 g) gelatins are used in conjunction with the capsulation of hygroscopic vehicles or solids, and standard gelatin formulas can be modified so as to require up to 50% less water for satisfactory operation on the capsulation machine. These modified formulas afford less opportunity for the hygroscopic fill materials to attract water from the shell and thereby improve the ingredient and physical stability of the product.[7]

Iron is always present in the raw gelatin, and its concentration usually depends on the iron content of the large quantities of water used in its manufacture. Gelatins used in the manufacture of soft gelatin capsules should not contain more than 15 ppm of this element, because of its effect on Food, Drug, and Cosmetic (FD&C) certified dyes and its possible color reactions with organic compounds.

The *plasticizers* used with gelatin in soft capsule manufacture are relatively few. Glycerin USP, Sorbitol USP, Pharmaceutical Grade Sorbitol Special, and combinations of these are the most prevalent. The ratio by weight of dry plasticizer to dry gelatin determines the "hardness" of the gelatin shell, assuming that there is no effect from the capsulated material. (Some examples of glycerin/gelatin ratios are shown in Table 13-2 along with their typical usage.) The ratio by weight of water to dry gelatin can vary from 0.7 to 1.3 (water) to 1.0 (dry gelatin) depending on the viscosity of the gelatin being used. For most formulations, however, it is approximately 1 to 1. Since only water is lost during the capsule drying process, the percentage of plasticizer and gelatin in the shell is increased, but the important plasticizer to gelatin ratio remains unchanged.

In general, the additional *components* of the gelatin mass are limited in their use by (1) the

TABLE 13-2. *Typical Shell "Hardness" Ratios and Their Uses*

Hardness	*Ratio Dry Glycerin/ Dry Gelatin*	*Usage*
Hard	0.4/1	Oral, oil-based, or shell-softening products and those destined primarily for hot, humid areas.
Medium	0.6/1	Oral, tube, vaginal oil-based, water-miscible-based, or shell-hardening products and those destined primarily for temperate areas.
Soft	0.8/1	Tube, vaginal, water-miscible-based or shell-hardening products and those destined primarily for cold, dry areas.

amounts required to produce the desired effect; (2) their effect on capsule manufacture; and (3) economic factors. Examples of ingredients falling into the first two categories are shown in Table 13-3.

The addition of *medicaments* to the gelatin mass usually is not recommended, for economic reasons, since only 50% of the gelatin mass is incorporated into the capsules. This results in a 50% loss of the added medicament. However, certain highly active, relatively inexpensive compounds such as benzocaine (3 mg/capsule shell) in chewable cough capsules may be used successfully.

Additional comments relative to the *color* of the gelatin shell are in order, since color is such an important aspect of all products. This is particularly true of soft gelatin capsules, in which the color of the capsule can be definitely affected by the color or type of material capsulated. As a general policy, the color of the capsule shell should never be lighter in hue than the capsulated material.

More specifically, darker colors are more appropriate for large-size (14 to 20 minim oblong) oral products, since they will not accentuate the size. Also, before a color is chosen, mixtures should be checked in the laboratory by addition of water to ascertain if reactions take place to cause the mixture to darken, as in the case of ascorbic acid and iron salts in vitamin and mineral formulations, or as in the case of reactions between iron and compounds of a phenolic nature. Since iron is present in gelatin, dark spots may occur in the shell owing to the migration of water-soluble iron-sensitive ingredients from the fill material into the shell. As a rule, clear colors usually are employed with clear type fill materials, and opaque colors are used with suspensions, but the reverse of this rule can be chosen to achieve a particular appearance or for ingredient stability purposes. For special effects or identification purposes, two colors, both opaque or one opaque and one clear, may be chosen since the manufacturing process involves two gelatin films.

A publication by Hom and co-workers describes a gelatin disk method for the determination of the effects of agitation, temperature, dissolution medium, and shell composition on the dissolution rate of soft gelatin capsules.[8] This information should be helpful in the formulation of gelatin capsules for various purposes.

From the foregoing discussion on the gelatin shell, one may conclude that the pharmaceutical chemist must rely heavily on the experience of the custom capsule manufacturer. However, in order to choose the proper gelatin, gelatin formula, and color, the custom manufacturer must rely on the technical and product information designed and developed by the pharmaceutical chemist. With such mutual cooperation and free exchange of information, new products or dosage forms can be efficiently developed.

TABLE 13-3. *Additional Components of the Gelatin Mass*

Ingredient	*Concentration*	*Purpose*
Category I		
Methylparaben, 4 parts; Propylparaben, 1 part	0.2%	Preservative
FD&C and D&C water-soluble dyes, certified lakes, pigments, and vegetable colors, alone or in combination	q.s.	Colorants
Titanium dioxide	0.2 to 1.2%	Opacifier
Ethyl vanillin	0.1%	Flavoring for odor and taste
Essential oils	to 2%	Flavoring for odor and taste
Category II		
Sugar (sucrose)	to 5%	To produce chewable shell and taste
Fumaric acid	to 1%	Aids solubility; reduces aldehydic tanning of gelatin

The Nature of the Capsule Content

Soft gelatin capsules can be used to dispense a variety of liquids and solids. Requirements and specifications of these materials vary, depending on the equipment of the manufacturer, but there are basic precepts that may be used as a guide for the formulation and production of commercially and therapeutically acceptable capsules, regardless of method of capsulation. The formulation of the capsule content for each product is individually developed to fulfill the specifications and end-use requirements of the product.

Except for the Accogel process, which is primarily concerned with the capsulation of dry

powders, the content of a soft gelatin capsule is a liquid, or a combination of miscible liquids, a solution of a solid(s) in a liquid(s), or a suspension of a solid(s) in a liquid(s). All such materials for capsulation are formulated to produce the smallest possible capsule consistent with maximum ingredient and physical stability, therapeutic effectiveness, and production efficiency. Once the smallest capsule size is determined, personnel in the sales or marketing departments usually choose the color, shape, and ultimate size of the retail product, unless there is a technical or production reason for the development chemist to specify a particular size, shape, and color. The maximum capsule size and shape for convenient oral use in humans is the 20 minim oblong, the 16 minim oval, or the 9 minim round as shown in Figure 13-26.

Liquids are an essential part of the capsule content. Only those liquids that are both water-miscible and volatile cannot be included as major constituents of the capsule content since they can migrate into the hydrophilic gelatin shell and volatilize from its surface. Water, ethyl alcohol, and, of course, emulsions fall into this category. Similarly, gelatin plasticizers such as glycerin and propylene glycol cannot be major constituents of the capsule content, owing to their softening effect on the gelatin shell, which thereby makes the capsule more susceptible to the effects of heat and humidity. As minor constituents (up to about 5% of the capsule content), water and alcohol can be used as cosolvents to aid in the preparation of solutions for capsulation. Also, up to 10% glycerin and/or propylene glycol can be used as cosolvents with polyethylene glycol or other liquids that have a shell-hardening effect when capsulated alone.

There are a large number of liquids that do not fall into the foregoing category and thus can function as active ingredients, solvents, or vehicles for suspension-type formulations. These liquids include aromatic and aliphatic hydrocarbons, chlorinated hydrocarbons, and high-molecular-weight alcohols, esters, and organic acids. Many of these are used in veterinary, cosmetic, and industrial products. For human use, however, the pharmaceutical chemist is often limited in his selection or use of a particular liquid because of government regulations, product performance specifications, ingredient incompatibilities, and liquid-solid adsorption characteristics. The most widely used liquids for human use are oily active ingredients (clofibrate), vegetable oils (soybean oil), mineral oil, nonionic surface active agents (polysorbate 80), and polyethylene glycols (400 and 600), either alone or in combination. Such active ingredient oils as fish oil may also function as a solvent, or as the suspending medium for one or more additional active ingredients, as in vitamin capsules.

All liquids, solutions, and suspensions for capsulation should be homogeneous and air-free (vide infra), and preferably should flow by gravity at room temperature, but not at a temperature exceeding 35°C at the point of capsulation, since the sealing temperature of the gelatin films is usually in the range of 37 to 40°C. In general, liquids ranging in *viscosity* from ethyl ether (0.222 cp at 25°C)[9] to heavy adhesive mixtures (exceeding 3000 cp at 25°C) may be encapsulated, but there are some exceptions since the property of viscosity alone is not the sole criterion. Liquids that exhibit the rheologic property of tack or tackiness, such as glycerin (954 cp at 25°C),[9] are exceptions, since such liquids can eventually cause the binding of slide valves and pumps in the capsule filling mechanism. Also, preparations for encapsulation should have a pH between 2.5 and 7.5, since preparations that are more acidic can cause hydrolysis and leakage of the gelatin shell, and preparations that are more alkaline can tan the gelatin and thus affect the solubility of the shell.

The capsulation of water-immiscible liquids is the simplest form of soft gelatin capsulation and usually requires little or no formulation. The minimum size capsule depends on the dosage desired, the minimum fill volume being calculated from the specific gravity of the liquid. A die size and shape may then be chosen from those shown in Figure 13-26. The nearest die size above the calculated fill volume may be used, or any larger die may be chosen if the active ingredient is to be diluted for some reason. For example, a 25,000-unit vitamin A capsule using vitamin A palmitate (1,000,000 units A/g) as a source for the vitamin A would have a minimum fill volume of about 0.45 minims, and thus could be diluted to any size capsule desired. On the other hand, the same potency capsule using fish oil (50,000 units A/g) as a source for the vitamin A would have a minimum fill volume of about 8.8 minims.

The minimum fill volume for water-miscible, nonvolatile liquids, such as polysorbate 80, is determined in the same manner. Because of their hygroscopic nature, however, they cause water to migrate from the gelatin shell into the fill material. This migration is rapid and could amount to 20% of the weight of the miscible liquid. During the drying period of the capsule, most of this water returns to and passes through the gelatin shell, but up to 7.5% of the original water can remain in the fill material, depending

on the hydrophilic properties of the liquid. Thus, for liquids of this type, a safety factor must be used in establishing the minimum fill volume and in choosing the die.*

Although oily liquids do not retain moisture, water does pass from the shell of the capsule into the fill material and out again during the manufacture and drying of these capsules. This is important for the formulator to remember, since such water transfer can and does have a bearing on formulations in which oily liquids are used as solvents or as vehicles for suspensions. If such suspensions contain hydrophilic solids, water may be retained up to 3% by weight of the hydrophilic material.

Combinations of miscible liquids often are used to produce desired physiological results such as increased or more rapid absorption of active ingredient (vitamin A and polysorbate 80); or to produce desired physiochemical results, such as improved flow properties (dilution or partial substitution with a thinner liquid), or improved solubility (steroid with oil and benzyl alcohol).

Except for when the Accogel process is used, solids are filled into soft gelatin capsules, in the form of either a solution or a suspension. The preparation of a suitable solution of a solid medicament should be the first goal of the pharmaceutical chemist. Usually, a solution is more easily capsulated and exhibits better uniformity, stability, and biopharmaceutical properties than does a suspension. For oral products, the medicament must have sufficient solubility in the solvent system so that the necessary dose is contained in a maximum fill volume of 16 to 20 minims (1 to 1.25 cc).

Solids that are not sufficiently soluble in liquids or in combinations of liquids are capsulated as suspensions. Most organic and inorganic solids or compounds may be capsulated. Such materials should be 80 mesh or finer in particle size, owing to certain close tolerances of the capsulation equipment and for maximum homogeneity of the suspension. Many compounds cannot be capsulated, owing to their solubility in water and thus their ability to affect the gelatin shell, unless they are minor constituents of a formula or are combined with a type of carrier (liquid or solid) that reduces their effect on the shell. Examples of such solids are strong acids (citric), strong alkalies (sodium salts of weak acids), salts of strong acids and bases (sodium chloride, choline chloride), and ammonium salts. Also, any substance that is unstable in the presence of moisture (e.g., aspirin) would not exhibit satisfactory chemical stability in soft gelatin capsules.

The capsulation of *suspensions* is the basis for the existence of a large group of products. Again, the design of suspension type formulations and the choice of the suspending medium are directed toward producing the smallest size capsule having the characteristics previously described, i.e., maximum production capacity consistent with maximum physical and ingredient stability and therapeutic efficacy.

The formulation of suspensions for capsulation follows the basic concepts of suspension technology. Formulation techniques, however, can vary depending on the drug substance, the desired flow characteristics, the physical or ingredient stability problems, or the biopharmaceutical properties desired. In most instances, these techniques must be developed through the ingenuity of the formulating chemist; however, in the formulation of suspensions for soft gelatin encapsulation, certain basic information must be developed to determine minimum capsule size.

One laboratory tool for this purpose is known as the "base adsorption" of the solid(s) to be suspended. Base adsorption is expressed as the number of grams of liquid base required to produce a capsulatable mixture when mixed with one gram of solid(s). The base adsorption of a solid is influenced by such factors as the solid's particle size and shape, its physical state (fibrous, amorphous, or crystalline), its density, its moisture content, and its oleophilic or hydrophilic nature.

In the determination of base adsorption, the solid(s) must be completely wetted by the liquid base. For glycol and nonionic type bases, the addition of a *wetting agent* is seldom required, but for vegetable oil bases, complete wetting of the solid(s) is not achieved without an additive. Soy lecithin, at a concentration of 2 to 3% by weight of the oil, serves excellently for this purpose, and being a natural product, is universally accepted for food and drug use. Increasing the concentration above 3% appears to have no added advantage.

A practical procedure for determining base adsorption and for judging the adequate fluidity of a mixture is as follows. Weigh a definite amount (40 g is convenient) of the solid into a

*For example, a capsule to contain 500 mg of Polysorbate 80 would have a calculated $\left(\frac{0.5\text{g} \times 16.23 \text{ minim}}{1.08\text{g}}\right)$ fill volume of about 7.5 minims. Assuming, however, that there is 5% residual water in the dry capsule, the final fill volume would be about 8 minims $\left(\frac{.525\text{g} \times 16.23 \text{ minim}}{1.08\text{g}}\right)$.

150-ml tared beaker. In a separate 150-ml tared beaker, place about 100 g of the liquid base. Add small increments of the base to the solid, and using a spatula, stir the base into the solid after each addition until the solid is thoroughly wetted and uniformly coated with the base. This should produce a mixture that has a soft ointment-like consistency. Continue to add liquid and stir until the mixture flows steadily from the spatula blade when held at a 45-degree angle above the mixture. The flow is even and continuous, and not in "globs." Attention also should be given to the nature of the "cut-off" quality of the mixture. As the mixture tends to stop flowing, proper cut-off is exhibited when the stream contracts rapidly upward toward the spatula blade rather than "stringing out" in intermediate flow.

At the conclusion of the foregoing test, the base adsorption is obtained by means of the following formula:

$$\frac{\text{Weight of Base}}{\text{Weight of Solid}} = \text{Base Adsorption}$$

The base adsorption mixture is milled or homogenized, and deaerated (a desiccator under vacuum is suitable), and the specific gravity is taken. The specific gravity is the weight of mixture (W) per cubic centimeter or per 16.23 minims (V). As in the case of liquids and solutions, the specific gravity may be used to determine the die size required for a given quantity of the particular mixture.

The base adsorption is used to determine the "minim per gram" factor (M/g) of the solid(s). The minim per gram factor is the volume in minims that is occupied by one gram (S) of the solid plus the weight of liquid base (BA) required to make a capsulatable mixture. The minim per gram factor is calculated by dividing the weight of base plus the gram of solid (BA + S) by the weight of mixture (W) per cubic centimeter or 16.23 minims (V). A convenient formula is:

$$\frac{(BA + S) \times V}{W} = M/g$$

Thus, the lower the base adsorption of the solid(s) and the higher the density of the mixture, the smaller the capsule will be. This also indicates the importance of establishing specifications for the control of those physical properties of a solid mentioned previously that can affect its base adsorption.

The BA and M/g data need not be obtained on any material that is to be capsulated alone at concentrations of 50 mg or less, since the smallest capsules can accommodate such quantities. If such material is to be used in combination, however, the data become necessary to allow for its inclusion in the formulation. The convenience of using M/g factors is particularly evident in the vitamin field, where there may be many ingredients and numerous combinations. Since the minim per gram factors are additive, they can be used for a more rapid calculation of capsule size than can be given by the preparation of the many possible mixtures in the laboratory. See Table 13-4 for BA and M/g data on some typical solids.

The final formulation of a suspension invariably requires a *suspending agent* to prevent the settling of the solids and to maintain homogeneity prior to, during, and after capsulation. The nature and concentration of the suspending agent vary, depending on the job to be done. Also, a rather delicate balance must be achieved between the requirement for a stable suspension and the requirement for the mixture to have the proper flow characteristics. There is evidence, too, that the proper suspending agent coats the suspended solids, imparting a certain lubricity to them and thereby aiding capsulation. Also, the coating can prevent contact with possible incompatible components in the mixture. Of the examples shown in Table 13-5, the most widely used suspending agent for oily bases is wax mixture, and in nonoily bases, the polyethylene glycols 4000 and 6000.

In all instances, the suspending agent used is melted in a suitable portion of the liquid base, and the hot melt is added slowly, with stirring, into the bulk portion of the base, which has been preheated to 40°C prior to the addition of any solids. The solids are then added, one by one, with sufficient mixing between additions to ensure complete wetting. Incompatible solids are added as far apart as possible in the mixing order to prevent interaction prior to complete wetting by the base.

Additional aids to formulation involve the physical and ingredient stability of the capsules. There should be little concern with oxidation or the effects of light as a cause of ingredient instability, since the gelatin shell is an excellent oxygen barrier and may be opacified.[10,11]

Most ingredient stability problems are associated with the available moisture from the gelatin shell, which when absorbed into the capsule content, can cause areas of high concentration of water-soluble solids, leading to ionization and interaction of the solids. Such problems may be alleviated or eliminated by employing a less soluble salt (procaine penicillin instead of potas-

TABLE 13-4. *BA and M/g Factors of Some Typical Solids*

Ingredient	*Base**	*BA*	*M/g*
Acetaminophen	Veg. oil	0.76	25.97
Acetaminophen	PEG 400	0.75	23.07
Ascorbic acid	Veg. oil	0.60	20.60
Ascorbic acid	Polysorbate 80	1.10	26.92
$Al(OH)_3$—$MgCO_3$ (FMA 11)	Veg. oil	1.90	41.30
$Al(OH)_3$—$MgCO_3$ (FMA 11)	PEG 400	2.44	42.10
Danthron	Veg. oil	1.30	33.75
Danthron	Glyceryl monooleate	1.39	33.94
Danthron	Polysorbate 80	1.38	31.28
Danthron	PEG 400	1.60	33.62
Danthron	Triacetin	1.83	36.02
Ephedrine SO_4	Veg. oil	1.30	36.80
Ferrous SO_4 exsiccated	Veg. oil	0.30	10.60
Ferrous SO_4 exsiccated	Polysorbate 80	0.47	12.90
Guaifenesin	Veg. oil	1.28	34.68
Lactose	Veg. oil	0.75	23.87
Desiccated liver	Veg. oil	0.80	25.70
Mephenesin	Veg. oil	2.50	57.38
Mephenesin	PEG 400	2.13	44.77
Meprobamate	Veg. oil	1.59	42.55
Meprobamate	PEG 400	1.30	32.52
Niacinamide	Veg. oil	0.80	25.63
Neomycin sulfate	Veg. oil	0.60	20.66
Phenobarbital	Veg. oil	1.20	33.60
Procaine penicillin G	Veg. oil	0.91	28.63
Sodium ascorbate	Veg. oil	0.76	22.40
Salicylamide	Veg. oil	0.80	25.80
Sulfathiazole	Veg. oil	0.43	17.90
Sulfanilamide	Veg. oil	1.03	28.55
Tetracycline (amphoteric)	Veg. oil	0.61	21.63

*Vegetable oil bases contain 3% soy lecithin.

sium), employing coatings (gelatin-coated B_{12}), adjusting pH with appropriate small quantities of citric, lactic, or tartaric acids or with less restrictive quantities of sodium ascorbate or magnesium oxide, or salting-out with appropriate small quantities of sodium chloride or sodium acetate.

Usually, the *physical stability* of a product is associated primarily with the type of gelatin and gelatin formulation used but can be aided by proper fill formulation. If a particular solid may have a deleterious action on the gelatin shell, the form of the solid that is least water-soluble and the most oleophilic would be the form of

TABLE 13-5. *Typical Suspending Agents*

Type	*Concentration of Oily Base (%)*	*Type*	*Concentration of Nonoily Base (%)*
White wax, NF	5	Polyethylene glycol 4000 and 6000	1–15
Paraffin wax, NF	5	Solid nonionics	10
Animal stearates	1–6	Solid glycol esters	10
Wax mixture*	10 and 30	Acetylated monoglycerides	5
Aluminum monostearate, NF†	3–5		
Ethocel (100 cps)†	5–10		

*1 part hydrogenated soybean oil: 1 part yellow wax, NF; 4 parts vegetable shortening (melting point 33 to 38°C): used at 10% on the adsorption oil and at 30% on any filler oil required.

†Used with volatile organic liquids such as butyl chloride; toluene; tetrachlorethylene; benzene.

choice for an oil-based suspension. An example would be the use of calcium salicylate rather than the sodium or magnesium salts. Also, the type of liquid base used can have an effect on physical stability. For example, the proteolytic effect of chloral hydrate on the gelatin shell is greatly reduced when a polyethylene glycol base is used in place of an oily base.

With the proper selection of materials and formulation techniques, the pharmaceutical chemist can prepare solutions or suspensions for comparisons of stability and dissolution rate with formulations of other solid dosage forms. By accurately filling two-piece gelatin capsules with such formulations, comparative absorption, urinary excretion, and metabolic studies can be made prior to the actual preparation of the soft gelatin capsule dosage form. Today the product development laboratory must evaluate all potential formulations for a new drug substance or for product improvement.

Capsule Manufacture, Processing, and Control

Although this aspect of soft gelatin capsules is the primary responsibility of the custom manufacturer, the pharmaceutical chemist should have an understanding of the materials and equipment involved in the capsule's manufacture, processing, and quality control. The several methods of capsulation referred to in the early part of this chapter, although differing somewhat in mechanical principles, do require the use of similar materials, processing steps, and equipment, and the use of equivalent control procedures.

Except for the gelatin preparation department, the manufacturing areas of a typical plant are air-conditioned to assure the proper conditioning of the gelatin films, the proper drying of the capsules, and the consistent low moisture content of raw materials and mixtures. The temperature is usually in the range of 20 to 22°C, and the humidity is controlled to a maximum of 40% in the operating areas and a range of 20 to 30% in the drying areas.

In the *gelatin preparation* department of a typical manufacturer, the gelatin is weighed on printomatic scales and mixed with the accurately metered (printomatic) and chilled (7°C) liquid constituents in suitable equipment, such as a Pony Mixer. The resultant fluffy mass is transferred to melting tanks and melted under vacuum (29.5" Hg) at 93°C. The mixing process requires about 25 min for 270 kg of mass, and the melting procedure requires about 3 hours. A sample of the resulting fluid mass is visually compared with a color standard, and additional colorants are blended into the mass if adjustments are required. The mass is then maintained at a temperature of 57 to 60°C before and during the capsulation process.

The *materials preparation* department will have a weigh-off and mixing area containing the necessary equipment and facilities for the preparation of the variety of mixtures that may be capsulated. Typical equipment would include printomatic scales for exacting measurements and control records; stainless-steel jacketed tanks for handling from 10- to 450-gallon batches of mix; and mixers, such as the Cowles, for the initial blending of solids with the liquid base. After the initial blending is completed, the mixture is put through a *milling* or *homogenizing* process, using equipment such as the homoloid mill, stone mill, hopper mill, or the Urschel Comitrol. The purpose of the milling operation is not to reduce particle size, but to break up agglomerates of solids and to make certain that all solids are "wet" with the liquid carrier, so as to achieve a smooth and homogenous mixture.

Following the milling operation, all mixtures are subjected to *deaeration*, and particularly so if the capsulation machine is equipped with a positive displacement pump. Deaeration is necessary to achieve uniform capsule fill weights; it also protects against loss of potency through oxidation prior to and during capsulation. When small amounts of volatile ingredients are included in a formulation, they are carefully added and blended into the bulk mixture after deaeration. Most liquids and suspensions may be deaerated by means of equipment designed to expose thin layers of the material continuously to a vacuum (29.5" Hg) and at the same time transfer the material from the mixing tank to the container that will be used at the capsulation machine. Suspensions or liquid mixtures containing volatile liquids or liquid surface active agents as chief constituents of the formula may be deaerated by subjection to temperatures up to 60°C for the period required to achieve the results desired. After deaeration, the mixture is ready to be capsulated.

At this point, samples of the mixture are often sent to the quality control laboratory for various tests, such as ingredient assays and specific gravity, and tests for homogeneity of suspension, moisture content, or air entrapment. This in-process quality control step may or may not be routine, depending on the product or anticipated problems, but should always occur with new products until the process is validated.

Owing to space limitations, a detailed description of each capsulation process is not possible. A schematic drawing of the rotary die process is presented, however, to acquaint the pharmaceutical chemist with the fundamental aspects of capsulation (Fig. 13-27). The gelatin mass is fed by gravity to a metering device (spreader box), which controls the flow of the mass onto air-cooled (13 to 14°C) rotating drums. Gelatin ribbons of controlled (±10%) thickness are formed. The wet shell thickness may vary from 0.022 to 0.045 inch, but for most capsules, it is between 0.025 and 0.032 inch. Thicker shells are used on products requiring greater structural strength. Product cost is directly proportional to shell thickness. The ribbons are fed through a mineral oil lubricating bath, over guide rolls, and then down between the wedge and the die rolls.

The material to be capsulated flows by gravity into a positive displacement pump. The pump accurately meters the material through the leads and wedge and into the gelatin ribbons between the die rolls. The bottom of the wedge contains small orifices lined up with the die pockets of the die rolls. The capsule is about half sealed when the pressure of the pumped material forces the gelatin into the die pockets, where the capsules are simultaneously filled, shaped, hermetically sealed, and cut from the gelatin ribbon. The sealing of the capsule is achieved by mechanical pressure on the die rolls and the heating (37 to 40°C) of the ribbons by the wedge.

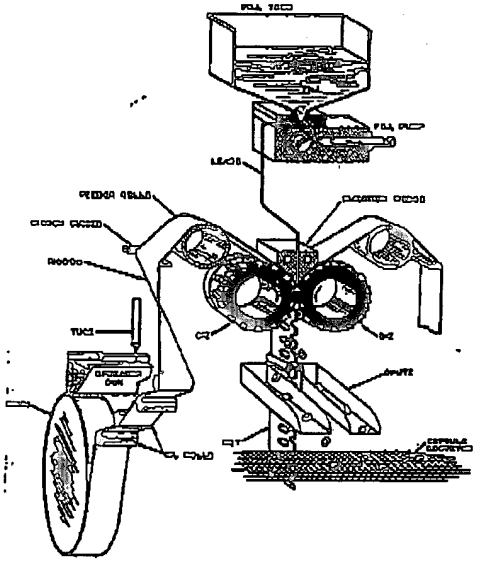

FIG. 13-27. *Schematic drawing of rotary die process. (Courtesy of R.P. Scherer Corporation, Troy, MI.)*

During manufacture, capsule samples are taken periodically for seal thickness and fill weight checks. The seals are measured under a microscope, and changes in ribbon thickness, heat, or die pressure are made if necessary. Acceptable seal thickness is one half to two thirds of the ribbon thickness. Fill weight checks are made by weighing the whole fresh capsule, slitting it open, and expressing the contents. The shell is then washed in a suitable solvent (petroleum ether), and the empty shell is reweighed. If necessary, adjustments in the pump stroke can be made to obtain the proper fill weight.

Immediately after manufacture, the capsules are automatically conveyed through a naphtha wash unit to remove the mineral oil lubricant. The washed capsules may be automatically subjected to a preliminary infrared drying step, which removes 60 to 70% of the water that is to be lost, or may be manually spread directly on trays. Capsules from the infrared dryer are also spread on trays, and all capsules are allowed to come to equilibrium with forced air conditions of 20 to 30% relative humidity at 21 to 24°C.

Capsules at equilibrium with 20 to 30% RH at 21 to 24°C are considered "dry," and the shell of such a capsule contains 6 to 10% water, depending on the gelatin formula used. The moisture content of the shell is determined by the toluene distillation method, collecting the distillate over a period of one hour. Additional water may be removed from "dry" capsules by further heating, e.g., at 40°C, but such a manufacturing step has not been found to be practical or necessary.

After drying, the capsules are transferred to the inspection department and held until released by the quality control department. The *inspection and quality control* steps in the processing of capsules are much the same as with other dosage forms and must conform to good manufacturing practice. Control tests specifically applicable to the quality of soft gelatin capsules may involve seal thickness determinations, total or shell moisture tests, capsule fragility or rupture tests, and the determination of freezing and high temperature effects.

Also, capsules may be sent after drying to a finishing department for heat branding or ink printing for purposes of identification.

Final physical control processing and packaging may be accomplished by the following in-line continuous operations.

1. A capsule diameter sorter allows to pass to the next unit any capsule within ±0.020 inch of the theoretic diameter of the particular capsule being tested. Overfills, underfills, and "foreign"